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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/775,964	02/10/2004	Jia-Hwa Fang	PP16502.015	1609
7590 05/13/2009				
Alisa Harbin, Esq. Novartis Vaccines and Diagnostics, Inc. Intellectual Property - R440 P. O. Box 8097 Emeryville, CA 94662				
EXAMINER				
FUBARA, BLESSING M				
ART UNIT		PAPER NUMBER		
1618				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/775,964

Applicant(s)

FANG ET AL.

Examiner

BLESSING M. FUBARA

Art Unit

1618

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 2/12/09.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 34-42 and 62-76 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 34-42 and 62-76 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/06)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

The examiner acknowledges receipt of request for continued examination under 37 CFR 1.114, amendment remarks filed 2/12/09. Claims 34, 37 and 39 are amended are amended. Claims 34-42 and 62-76 are pending.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/12/09 has been entered.

Response to Arguments

Previous rejections that are not reiterated herein are withdrawn. Paliard is dropped in the rejections in view of applicant's statement of common ownership. O'Hagan is also dropped as an anticipatory art.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 70 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is written description.

5. Claims 70 is dependent on claim 34 which stipulates that the microparticles are not subjected to a washing step. Example 6 of the instant specification supports a non-washing technique. The rest of the embodiments in the specification washes the particles and also subjects the particles to centrifugation step. However, there is no description for the “Non-washing Technique” to exclude centrifugation as a wash step. Thus, the specification as filed does not have possession for a process of making microparticles in the “Non-washing Technique” without centrifugation. The limitation of claim 70, which further limits the invention of claim 34 is not envisioned at the time of the application was filed.

The rejection may be overcome by removing what was not envisioned at the time of filing from claim 70.

6. Claim 70 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 70 is unclear in the context of claim 34 upon which it depends. Specifically, claim 34 excludes a wash step. For claim 70 to further limit the claim to exclude washing by centrifugation appears to impart that there is a wash step in claim 34 except for the was step that is carried out by centrifugation.

8. Correction and/or explanation is respectfully requested.

Claim Rejections - 35 USC § 103

9. Claims 34-42 and 62-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al. (US 6,395,253) in view of O'Hagan et al. (WO 00/50006) or Van Nest (US 2001/0046967).

10. Claims 34, 37 and 39 are amended to indicate in item (c) that "10-90% of the total detergent in the microparticle composition is bound to the microparticle and the remainder is unbound," but this new addition to claim appears to be a repetition of the last two lines of (b). Therefore, the repetition of what is already present does not change the scope of the claims.

LEVY discloses preparation of microspheres that contain DNA or RNA as the bioactive agent (column 4, lines 31, 54 and 55). LEVY prepares a double emulsion of water-in-oil-in-water emulsion by using a condensing agent in one phase and the method comprises the steps of: "(a) dissolving at least one polymer in a water-immiscible organic solvent to yield an organic phase; (b) dissolving a polyanionic bioactive agent in aqueous solution to yield a first aqueous phase; (c) emulsifying the organic and first aqueous phases to yield a first milky emulsion; (d) dissolving a condensing agent in aqueous solution to yield a second aqueous phase; (e) emulsifying the first milky emulsion and the second aqueous phase to yield a second milky emulsion; and (f) removing the organic solvent from the second milky emulsion to yield microspheres containing condensed polyanionic bioactive agent with the emulsion meeting claims 34, 35 and 36-39. "The removal of the organic solvent in the final step is preferably by means of evaporation," in one illustrative embodiment (column 4, lines 44 and 45). DNA and RNA are macromolecules and are polynucleotides meeting the requirements of claims 74-76. The concept of microspheres meets the microparticle limitation of claims 34, 37, 39, 42, 62, 65-

70. Regarding the recitation that the microparticles are not subjected to washing step, it is noted that while the examples in Levy disclose a wash step, the basic preparation disclosed by Levy in section 4.2 does not state a wash step but rather that the microspheres are collected by ultracentrifugation and the alternative protocol disclosed in 4.6 and the comprising language is open. Levy uses 0.1% detergent (SDS in this case). There is no demonstration in applicants' specification that not subjecting the microparticles to a washing step provides unusual/unexpected results to the microparticles. The claims do not recite amount of detergent added to make the microparticle in the emulsion.

Regarding claim 36, which is directed to the process of cross-flow filtration, it is noted that in the cross-flow filtration process of the examined application, four liters of deionized water (Example 5) is used to remove the detergents and this appears to be equivalent to washing so that the cross-filtration step of the claim 34 reads on optional wash step of one of embodiments of Levy at column 13, line 5; at column 18, line 42 (washed with tris-EDTA); at column 20, line 2 (cells washed with PBS buffer). There is also no demonstration that the cross-filtration step performed after removing the organic solvent provides unusual results; Levy discloses filtration as one of the steps. The filtration step in Levy meets the filtration step in claims 34 and 37.

Regarding the ratio of lactide to glycolide, it is noted that there is no demonstration by applicants that the recited ratio provides unusual/expected results. The silence of Levy on the ratio of lactide to glycolide is an indication that the lactide/glycolide can be used in any desired ratio that would be effective as a condensing agent for the DNA or RNA macromolecules. Levy also teaches polypeptide (column 4, line 64) meeting claim 72 and the SDS meets claim 71.

Regarding new claims 68-70, Levy in one of the embodiments does not wash the product but removes the solvent from the emulsion by evaporation so that the detergent is not removed or washed off (column 12, lines 58-67).

Levy uses SDS detergent. While Levy does not specifically state the presence of bound detergent in the amounts recited in the claims, it is noted that Levy does not specifically state that the microspheres/particles formed are free of detergent; and it flows from one of the embodiment that does not use a wash step but evaporates off the organic solvent (column 12, lines 58-67) that the detergent is not removed and as such, the microparticles would have detergent associated. However, while Levy teaches SDS and TWEEN, Levy does not disclose the use of cetyl trimethyl ammonium bromide (CTAB) detergent. But emulsions containing microparticles comprising macromolecules such as polynucleotides and polypeptides, polymers such as poly(α -hydroxy acid), a polyhydroxy butyric acid, polycaprolactone, polyorthoester, polyanhydride and polycyanoacrylate, and cationic detergents such as CTAB are known in the art (see O'Hagan at page 7, last full paragraph, pages 8-11; Tables 19A and 19B; and page 2, 4th full paragraph). Thus O'Hagan is relied upon for a teaching that the specific CTAB detergent can be used with PLG in an emulsion with macromolecules. CTAB and the SDS meet the detergent limitations of claims 38, 40, 68, 71. Further also, Van Nest discloses that polynucleotides may be delivered in vehicles such as liposomes or emulsions made with cationic lipids or polymers, such as 1,2-dioleoyl-1,2,3-trimethylammonio propane (DOTAP), cetyltrimethylammonium bromide (**CTAB**) or polylysine (see paragraphs [0101], [0091], [0090], [0088] and [0086]). Therefore, taking the teachings of the references together, one having ordinary skill in the art at the time at the invention was made would have reasonable expectation of success that including the detergent

CTAB in the double emulsion of Levy would produce emulsion whose particles would effectively adsorb polynucleotides and polypeptides that would be expected to release/deliver the polynucleotide and the polypeptide as desired.

Response to Arguments

11. Applicant's arguments filed 2/12/09 have been fully considered but they are not persuasive.

12. Applicant argues that a) the teachings of Levy are not relevant to the pending claims because Levy does not describe as does the invention that 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder unbound and that prima facie case has not been made. The examiner disagrees with the applicant. Prima facie case was made and prima facie case is present. The artisan must determine that the amount of bound and unbound detergent and applicant has not determined that either less than 10-90% detergent is bound to the microparticles in the Levy art or that less than 10-90% is unbound of the total detergent in the microparticles. The biologically active molecule is adsorbed to the microparticles by incubation with the microparticles. By the same token, incubating or bringing together of contacting of the biological molecule with the microparticles in Levy should also result in adsorption of the biological molecules except applicant shows that the biologically active agents in Levy are not adsorbed and except there are other steps of adsorbing bio-molecules to particles that applicant has not claimed or disclosed that would prove superior to the contacting or incubation step described in applicants specification. The burden was on the applicant to factually show that the bio-molecules of Levy are not bound to the microparticles or that less than 10-90% of the total detergent in the microparticles are bound is bound and

unbound. “When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.” In *re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The examiner agrees with applicant that Levy is silent on whether the detergent is bound or unbound. But, applicant has not provided or disclosed or claimed specific methods that ensure binding and one that does not ensure binding.

13. b) Applicant further says that absent any reason, one of ordinary skill in the art would wash the microparticles of excess detergent by centrifugation as taught by Levy and that there is motivation in the art to do just that according to Singh. The examiner disagrees applicant’s attempt at re-writing the rejection of the claims in favor of washing. Applicant’s arguments presented in favor of a wash step is an opinion and does not take the place of factual evidence against Levy where the detergent would inherently bind to the microparticles following applicant’s process steps of binding detergent to microparticles. Furthermore, Levy did not report that absence of a wash step is detrimental to the DNA containing microparticles and since Levy did not suggest washing the microparticles, there would be no motivation to wash the microparticles. Again, the burden is on applicant to factually show otherwise.

14. c) Regarding filtration vs. washing, when the reference is considered as a whole, the broadest reasonable interpretation finds filtration is a form of washing and the evidence was presented and applicant disagrees with the evidence.

15. d) Applicant argues that Levy uses SDS to assess previously formed microspheres and even if this were the case, selection of any order of performing the process step is *prima facie* in the absence of new and unexpected results. In response to applicant’s dispute and request for

the legal authority, the references are i) 69 USPQ 330 (CCPA 1946), ii) 5 USPQ 230 (CCPA 1930) and 128 USPQ 440 (Bd. App. 19590 and thanks.

Applicant in argues against the individual references when a combination of references is used in the rejection. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

No claim is allowed.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).